METABOLISM OF ADRENALINE AND NORADRENALINE
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Adrenaline and noradrenaline have been shown until recently to be metabolized according to the following three mechanisms in vivo:

1) oxidative deamination of side chain by amine oxidase
2) oxidation of the phenolic group of the ring to form adrenaline-quinone and adrenochrome
3) conjugation of the phenolic group of the ring

Previous studies in our laboratory presented evidence for existence of a new enzyme named adrenaline dehydrogenase, which catalyzes the oxidation of adrenaline and noradrenaline to their keto forms, adrenalone or noradrenalone respectively (1-3). Moreover, adrenalone has been found in blood of rabbits (4). On the basis of these results, it has been assumed that a metabolic pathway of adrenaline and noradrenaline via adrenalone and noradrenalone may exist in vivo. This paper presents the results of a survey of the new metabolic pathway.

I. Excretion of Dihydroxyphenyl Derivatives into the Urine after the Administration of Adrenaline

In an attempt to pursue the metabolic trail of adrenaline in vivo, the urine of guinea pigs was analyzed by the procedure of paper chromatography after the administration of adrenaline.

Method

Guinea pigs, weighing about 200 g, were used. Each guinea pig was injected subcutaneously with 5 ml of adrenaline solution (100 μg/ml). The urine of these experimental animals was collected for 24 hours in a colored bottle, to which 7 ml of N-HCl and 5 drops of toluol were added previously. Then the collected urine was treated with alumina according to the method of Euler (5) as follows; 2.5 g of alumina was added to the urine adjusted to pH 8.5 with 0.1 N-NaOH. After shaking for 15 minutes, alumina was collected by centrifugation, washed 3 times with 10 ml of water, then the adsorbed compounds were eluted 3 times with 10 ml of 0.3 N-H₂SO₄. The elutes were combined and adjusted to pH 4.0 with 10% NaHCO₃. The solution was dried in vacuum and extracted 3 times with 10 ml of n-butanol. The butanol solution was dried in vacuum, and analyzed by the procedure of two dimension paper chromatography. The developing solvents were n-butanol-acetic acid-water (4 : 1 : 1) and phenol-water (77 : 23). Materials were located by spraying with AgNO₃ (6), ninhydrin reagent (7, 8), KI₀₃ (9, 10), Folin's reagent (11) or DNP reagent.*

* DNP reagent was prepared as follows; 0.5 g of 2,4-dinitrophenylhydrazine was added to 100 ml of 0.1 N-HCl, heated to resolve, then neutralized with dilute NaOH solution.
Results

As shown in Fig. 1, the normal urine indicated the presence of small amount of adrenaline but not adrenalone. While in the urine of animals injected adrenaline, the excretion of adrenaline and adrenalone was clearly demonstrated. These findings seem to present evidence for the conversion of adrenaline to adrenalone, suggesting that the adrenaline dehydrogenase responsible for this oxidation reaction may play an important role in the metabolism of adrenaline.

An increase excetration of protocatechuic aldehyde was also observed in the urine of guinea pigs after the administration of adrenaline, which appeared to implicate this compound as a metabolite of adrenaline. However the amount of the protocatechuic acid in the urine was not changed in this case.

All these data seemed to support the existence of the metabolic pathway of adrenaline via adrenalone in vivo, and the formation of protocatechuic aldehyde as a metabolite.

II. Metabolism of Adrenaline and Adrenalone in Liver Slices

Previous studies in this laboratory (1-3) and described in Chapter I suggested the oxidation of adrenaline to adrenalone, then the further fate of these compounds was studied in the next experiments. Liver slice of guinea pig was used for this purpose and the formed metabolites in the presence or absence of some enzyme inhibitors were assayed by the technique of paperchromatography.

Method

Freshly prepared liver slices of guinea pig were suspended in 2 ml of phosphate-Krebs-Ringer solution (pH 7.0), and 0.3 ml of 10⁻²M adrenaline or adrenalone, or 0.3 ml of 2 x 10⁻²M 3,4-dihydroxyphenylglyoxal was added as substrate. After the incubation of 3
hours at 37°C, the slices were removed, and the reaction mixture was adjusted to pH 3.0 with 0.1 N-HCl, then condensed. The obtained samples were applied for chromatographic development for 24 hours at room temperature with n-butanol-acetic acid-water (4:1:1), and materials were located by spraying with ammoniacal AgNO₃ (6), diazotized sulfanilic acid and Na₂CO₃, KIO₃ (9, 10), DNP reagent, Folin's reagent (11), ninhydrin reagent (7, 8).

KCN (10⁻⁴M), marsilid (10⁻⁵M) or hydroxylamine (10⁻⁵M) was used as enzyme inhibitor.

Results and Discussion

As shown in Fig. 2, paperchromatography of the reaction mixture with adrenaline resulted in many spots having different kinds of color as indicated in Table 1 at Rf 0.24, 0.28, 0.36, 0.50, 0.52, 0.61, 0.85 and 0.90.

When adrenalone was incubated with liver slices, similar spots were demonstrated except one spot at Rf 0.24. From the color and the Rf value of the spots observed on the paper chromatogram, these spots were presumed to be as shown in Table 2.

In the presence of marsilid, a potent inhibitor of amine oxidase, the spot (Rf 0.28) corresponding to adrenalone and another spot (Rf 0.52) were more definitely. And the all other spots corresponding to 3,4-dihydroxyphenylglyoxal (Rf 0.38), 3,4-dihydroxyphenylglyoxylic acid (Rf 0.61), protocatechuic acid (Rf 0.85) and protocatechuic aldehyde (Rf 0.90) were not formed, suggesting that these substances were formed by the action of amine oxidase on
adrenaline or its metabolite. As a metabolite of adrenaline having the amino group, the spot at Rf 0.28 corresponding to adrenalone and an unknown spot at Rf 0.52 were taken into consideration. The close similarities of the reaction products of adrenaline and adrenalone suggested the possibilities that adrenaline might be converted to adrenalone, then attacked by amine oxidase. The substances at Rf 0.52 has not been identified, but this substances arose from adrenaline or adrenalone and the formation of this substances was not due to the action of amine oxidase. This substance was tested for KIO₄-reaction, ninhydrin-Folin- and DNP-reaction with positive results, but for the reaction with p-dimethylaminobenzaldehyde, a reaction of indol ring, with negative.

In the presence of cyanide added as an inhibitor, the spots at Rf 0.24, 0.28, 0.38 and 0.53 appeared clearly but those at Rf 0.63, 0.83 and 0.90 were undistinctly as shown in Fig. 2. These results may suggest that adrenaline was converted to 3,4-dihydroxyphenylglyoxal through adrenalone and the presence of cyanide blocked the further metabolism of 3,4-dihydroxyphenylglyoxal. The block might be explained by an inhibition of aldehyde oxidase sensitive to cyanide or a formation of cyanhydrine with 3,4-dihydroxyphenylglyoxal.

In the experiments using 3,4-dihydroxyphenylglyoxal as substrate, four spots at Rf 0.36, 0.61, 0.83 and 0.90 were observed, and the addition of cyanide or hydroxylamine resulted in the occurrence of an unknown compound at Rf 0.28 which might be the result of cyanhydrine formation with 3,4-dihydroxyphenylglyoxal.

On the basis of the results described here the following reaction sequence might be postulated to take place in adrenaline metabolism.

### Table 1

<table>
<thead>
<tr>
<th>Rf</th>
<th>Ammoniacal AgNO₃</th>
<th>Diazotized sulfuric acid + Na₂CO₃</th>
<th>Nitroprusside Na + NaOH</th>
<th>1% KIO₄</th>
<th>2,4-Dinitrophenylhydrazine</th>
<th>Folin's reagent</th>
<th>Ninhydrin</th>
<th>p-Dimethylaminobenzaldehyde + HCl</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.90</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+(yellow)</td>
<td>±</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>0.85</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>±</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>0.65</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>±</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>0.52</td>
<td>+</td>
<td>+(orange-red)</td>
<td>+(red)</td>
<td>+(light red)</td>
<td>+(yellow)</td>
<td>+</td>
<td>+(pink-violet)</td>
<td>-</td>
</tr>
<tr>
<td>0.50</td>
<td>+</td>
<td>+</td>
<td>±</td>
<td>-</td>
<td>-</td>
<td>±</td>
<td>-</td>
<td>+(violet)</td>
</tr>
<tr>
<td>0.36</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+(yellow)</td>
<td>±</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>0.28</td>
<td>+</td>
<td>+(red-violet)</td>
<td>+(orange-red)</td>
<td>+(yellow-brown)</td>
<td>+(light-yellow)</td>
<td>+</td>
<td>+(pink-brown)</td>
<td>-</td>
</tr>
<tr>
<td>0.24</td>
<td>+</td>
<td>+(red-violet)</td>
<td>+(red)</td>
<td>+(violet-brown)</td>
<td>-</td>
<td>+</td>
<td>+(violet)</td>
<td>-</td>
</tr>
</tbody>
</table>

### Table 2

<table>
<thead>
<tr>
<th>Rf 0.90</th>
<th>Protocatechuic aldehyde</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.85</td>
<td>Protocatechuic acid</td>
</tr>
<tr>
<td>0.62</td>
<td>3,4-Dihydroxyphenylglyoxylic acid (?)</td>
</tr>
<tr>
<td>0.52</td>
<td>unknown</td>
</tr>
<tr>
<td>0.50</td>
<td>indole derivative</td>
</tr>
<tr>
<td>0.36</td>
<td>3,4-Dihydroxyphenylglyoxal</td>
</tr>
<tr>
<td>0.28</td>
<td>Adrenalone</td>
</tr>
<tr>
<td>0.24</td>
<td>Adrenaline</td>
</tr>
</tbody>
</table>
FIG. 3. Supposed metabolic pathway of adrenaline.

If the pathway of adrenaline metabolism through adrenalone could be demonstrated in slices consisting of intact cells, it would be assumed that this metabolic course might be probably operating in vivo, too.

III. Metabolism of β-C¹⁴-dl-Adrenaline and β-C¹⁴-Adrenalone in Vivo

In an attempt to obtain more definite information on the physiological pathway of adrenaline metabolism, β-C¹⁴-dl-adrenaline and β-C¹⁴-adrenalone, which were generously provided by Dr. R.W. Schayer, were used and the presence of radioactive substances in the urine was observed.

Method

Six healthy guinea pigs were divided into two groups and an animal belonging to each group was given an injection of 1γ of β-C¹⁴-dl-adrenaline or 1.5γ of β-C¹⁴-adrenalone per gram of body weight, respectively. The collected urine was treated and chromatographed as described in Chapter I.

The spots were located by spraying with ammoniacal AgNO₃ solution.

For the radioautography the paper chromatograms were pressed to Fuji industrial X-ray film type 400 at the both sides for 3-4 weeks. The paper chromatogram was cut into every 1 cm square and the radioactivity of each part was determined referring to the method of Tomalleri (12) with Geiger-Müller counter for 30 minutes and represented in c.p.m..

Results

Chromatography of the urine of the animal receiving adrenaline or adrenalone with the mixture of n-butanol-acetic acid, yielded only one more radioactive spot at Rf 0.80-0.88 corresponding protocatechuic acid and aldehyde. When the sample was developed with phenol-water, radioactivity was observed clearly at Rf 0.29 corresponding to protocatechuic acid. Some radioactivity was also found at Rf 0.80-0.95, suggesting the presence of radioactive adrenaline, adrenalone or protocatechuic aldehyde. These radioactive sites were in agreement with the spots visualized by spraying with AgNO₃. In some cases additional unidentified spots were observed at Rf 0.15 and 0.18 with phenol-water and at Rf 0.25 with butanol-acetic acid.
FIG. 4. Radioautogram on the developed filter papers of the urine of guinea pigs injected with radioactive adrenaline or adrenaone.

1) Adrenaline injected urine
IV. Metabolism of Noradrenaline and Noradrenalone in Liver Slices

The metabolism of noradrenaline which has similar structure to adrenaline and is one of the most physiologically important pressor amines has been assumed to be metabolically related to that of adrenaline. If this assumption is the case, protocatechuic acid would be expected to arise from noradrenaline in liver slices.

In the following experiments the conversion of noradrenaline to noradrenalone in liver slices was studied, together with the possible formation of protocatechuic acid, since it has been already known that noradrenaline is oxidized by amine oxidase.

Method

1) Conversion of noradrenaline to noradrenalone

Freshly prepared liver slices of guinea pigs or chicken were suspended in a medium composed of 2 ml of phosphate-Krebs-Ringer solution (pH 7.0), 0.3 ml of $10^{-5}$M noradrenaline and 0.2 ml of $10^{-3}$M marsilid. After incubation of 3 hours at $37^\circ C$, slices were removed and the reaction mixture was adjusted to pH 3.0, dried in vacuum. Then the resulting material was dissolved into a small amount of water and chromatographed with n-butanol:acetic acid:water = 4:1:1. The spot was located by spraying with 0.1% ninhydrin reagent or ammoniacal AgNO$_3$.

2) Formation of protocatechuic acid from noradrenaline

Fresh liver slices of guinea pigs or chicken were suspended in 2 ml of phosphate-Krebs-Ringer solution (pH 7.0) and 0.3 ml of $10^{-5}$M noradrenaline or noradrenalone was added as
After the incubation of 3 hours at 37°C, the reaction mixture was treated with alumina according to Euler’s method described in Chapter I. Then the components were eluted from alumina, extracted with n-butanol and dried in vacuum. The materials were developed with n-butanol : acetic acid : water = 4 : 1 : 1 for 18 hours at room temperature and the spot at Rf 0.81 corresponding to protocatechuic acid was cut off in 2 cm sq., extracted with n-butanol for rechromatography with phenol-water = 77 : 23.

Results

![Paperchromatogram of reaction product when adrenaline or noradrenaline was incubated with liver slices in the presence of marasilid.](image)

**FIG. 6.** Paperchromatogram of reaction product when adrenaline or noradrenaline was incubated with liver slices in the presence of marasilid.

<table>
<thead>
<tr>
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<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>0°C</td>
<td>37°C</td>
<td>0°C</td>
<td>0°C</td>
<td>37°C</td>
<td>6°C</td>
<td>37°C</td>
</tr>
</tbody>
</table>

**TABLE 3.** Colors and Rf values on the filter papers of adrenaline, noradrenaline, adrenalone and noradrenalone developed with n-butanol-acetic acid.

<table>
<thead>
<tr>
<th>Ninhydrin reagent</th>
<th>Adrenaline</th>
<th>Noradrenaline</th>
<th>Adrenalone</th>
<th>Noradrenalone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ammonialcal AgNO₃</td>
<td>violet-red</td>
<td>yellowish brown</td>
<td>pink-brown</td>
<td>dark brown</td>
</tr>
<tr>
<td>Rf value</td>
<td>0.29</td>
<td>0.24</td>
<td>0.34</td>
<td>0.27</td>
</tr>
</tbody>
</table>

As shown in Fig. 6 and Table 3, the color of the spot at Rf 0.27 presented clearly the conversion of noradrenaline to noradrenalone in liver slices.

The formation of protocatechuic acid from noradrenaline was indicated in Fig. 7.
When noradrenaline or noradrenalone was added to liver slices as substrate, reddish brown color was observed at Rf 0.25 by spraying with ammoniacal AgNO₃ after chromatographed with phenol-water, supporting the formation of protocatechuic acid. It has been demonstrated already that noradrenalone is oxidized by amine oxidase.

**FIG. 7.** Paperchromatography for the identification of protocatechuic acid.

When noradrenaline or noradrenalone was added to liver slices as substrate, reddish brown color was observed at Rf 0.25 by spraying with ammoniacal AgNO₃ after chromatographed with phenol-water, supporting the formation of protocatechuic acid. It has been demonstrated already that noradrenalone is oxidized by amine oxidase.

**FIG. 8.** Supposed metabolic pathway of adrenaline and noradrenaline.
From all of these findings together with the facts observed in the metabolism of adrenaline, it was considered that the pathway of noradrenaline metabolism was similar to that of adrenaline as shown in Fig. 8.

**DISCUSSION**

It is generally conceived that adrenaline is attacked by the following three reactions. 1) conjugation of the phenolic group of the ring, 2) oxidation of the phenolic group of the ring to form adrenochrome, 3) oxidative deamination of the side chain by monoamine oxidase.

As already reported by Richter (13), Beyer and Shapiro (14), Clark (15), Sato *et al.* (16), it has been clearly demonstrated that adrenaline is conjugated at the phenolic group of the ring. However this reaction is not observed except after the oral administration of a large amount of adrenaline. Experimental data reported by R.W. Schayer (17) showed this facts clearly, suggesting that this conjugation might not be expected to provide a main pathway for adrenaline metabolism.

The oxidation of the ring to form adrenochrome is observed non enzymatically, in alkali medium or in the presence of heavy metal ion such as Cu$^{++}$ and under various conditions, and also observed enzymatically by tyrosinase, polyphenolase, cytochrome system etc.. The existence of adrenaline oxidase, an enzyme of phenolase type, was assumed by Blaschko (18), Griesemer (19), Angenent and Koelle (20) and others, and was expected to associate with the action of adrenaline.

But the presence of adrenochrome has not been demonstrated in animal tissue. A possible explanation for this fact was furnished by non existence or by the unstableness of this compound. Specially the unstableness of adrenochrome, made it very difficult to determine whether adrenochrome is an intermediate in adrenaline metabolism or not. Schayer (21) injected a large amount of adrenochrome with $\beta$-$C$-$^{14}$-$dl$-adrenaline into rats but any shift of metabolic pattern of radioactive adrenaline was not observed. From these results, it has been supposed that the oxidation of the phenolic group of the ring to form adrenochrome may exist *in vivo*, but this route would not be a main pathway of adrenaline metabolism.

The next problem is to study the significance of amine oxidase in the metabolism of adrenaline. It has already been reported by Bernheim (22), Blaschko (23), Richter (24), Mann and Quastel (25), Philpot (26), Burn (27, 28) and others that adrenaline is oxidized by amine oxidase. Therefore this enzyme would be expected to concern with adrenaline metabolism to some extent in spite of some objections by Bacq (29), Euler (30) *et al.*. Schayer (17, 21, 31–34) presented interesting data on the relationship between amine oxidase and the metabolism of adrenaline. Fifty per cent of injected adrenaline was oxidized by amine oxidase. If adrenaline itself would be oxidized by amine oxidase, the following reaction sequence might take place, and 3,4-dihydroxymandelic acid would be expected to be formed through 3,4-dihydroxyphenylglycolaldehyde.
Moreover, if the metabolism of 3,4-dihydroxy-
mandelic acid is similar to the of mandelic acid,
the excretion of 3,4-dihydroxymandelic acid in the
urine would be demonstrated. However, the ex-
cretion of 3,4-dihydroxymandelic acid in the urine
as an end product of adrenaline has not been
reported. Schayer attempted to demonstrate its
excretion but no evidence was obtained.

Then, the possibility that adrenalone converted from adrenaline in the presence of ad-
renaline dehydrogenase may be attacked by amine oxidase was assumed. In the experi-
ments described by Schayer an unknown radioactive spot at RF 0.70 was observed in the
chromatogram of the urine of animals receiving radioactive adrenaline. This unknown spot
was supposed to have the amino group and to be adrenalone.

All of the results described in this paper presented evidence for the pathway shown in
Fig. 8 on the adrenaline metabolism.

If the pathway is the case, it would be postulated that a cleavage of a-carbon of adre-
naline is involved. However this assumption appeared to be unexplainable in terms of the
isotope data of Schayer with a-C\(^{14}\)-adrenaline, and moreover this assumption would suggest
the formation of protocatechuic acid, which was demonstrated in our paper. While Schayer
showed that radioactive protocatechuic acid was not excreted in the urine of rats administered
by \(\beta\)-C\(^{14}\)-dl-adrenaline. A possible explanation for this discrepancy would be furnished by
the following points; 1) guinea pig was used in this experiment, 2) the collected urine was
partially purified by treatment with alumina and extraction with n-butanol, then chromato-
graphed with the two different kinds of solvent, and many coloring reagents were used to
locate the spots.

The formation of protocatechuic acid from adrenaline was already suggested by Weinstein
and Mannig (35). They observed the excretion of protocatechuic acid in the urine of rabbits
receiving a large amount of adrenaline. Richter (13) and Bernheim (36) criticized these studies
and postulated that a part of adrenaline in the urine was converted to protocatechuic acid
during treating in the alkaline medium. Richter (13) also failed to show the excretion
of protocatechuic acid in the urine after adrenaline or epinine was administered orally to
himself. However recently Bray (37) obtained evidence for its excretion using the technique
of paperchromatography and coloring reactions.

In the present paper, the presence of protocatechuic acid was demonstrated in the normal
urine and the excretion of radioactive protocatechuic acid was also observed in the urine of
guinea pigs after the injection of radioactive adrenaline or adrenalone. Furthermore the
studies in vitro were carried out on the pathway and it was confirmed, both in vitro and in
vivo, that the products formed from adrenalone were always similar to those arising from
adrenaline, suggesting that the pathway of adrenaline via adrenalone might play an im-
portant role under physiological conditions.
A few experiments have been carried out on the metabolism of noradrenaline, which suggested the formation of noradrenalone and protocatechuic acid from noradrenaline in liver slices. If noradrenalone is converted from noradrenaline, it would be oxidized by amine oxidase to form 3,4-dihydroxyphenylglyoxal. This compound seems to be an intermediate metabolite of adrenaline and to be metabolized according to the same mechanism observed in the adrenaline metabolism to form protocatechuic acid as an end product.

SUMMARY

1. The excretion of adrenalone and protocatechuic aldehyde in the urine of guinea pigs was increased following an administration of adrenaline but the amount of protocatechuic acid remained at the same level with that in the normal urine.

2. The addition of adrenaline to liver slices resulted in the formation of adrenalone, 3,4-dihydroxyphenylglyoxal, protocatechuic aldehyde and protocatechuic acid, which were also found in case of adrenalone. When adrenaline and marsilid, a potent inhibitor of amine oxidase, were incubated, 3,4-dihydroxyphenylglyoxal, protocatechuic aldehyde and protocatechuic acid were not detected, and in the presence of adrenaline and potassium cyanide, protocatechuic aldehyde and protocatechuic acid were not formed.

   From 3,4-dihydroxyphenylglyoxal added as substrate, protocatechuic acid and protocatechuic aldehyde were formed.

3. Radioactive adrenaline, adrenalone, protocatechuic aldehyde and protocatechuic acid were formed in the urine of guinea pigs receiving $\beta$-C$^{14}$-dl-adrenaline. From $\beta$-C$^{14}$-adrenalone, the formation of radioactive protocatechuic aldehyde and protocatechuic acid was demonstrated.

4. In the presence of marsilid, the conversion of noradrenaline to noradrenalone was observed in liver slices. Moreover, protocatechuic acid was formed when noradrenaline or noradrenalone was added to liver slices.

5. From the results described here a new metabolic pathway of adrenaline and noradrenaline was discussed.

Acknowledgement. The authors wish to express their gratitude to Dr. R.W. Schayer for his donation of $\beta$-C$^{14}$-dl-adrenaline and $\beta$-C$^{14}$-adrenalone.

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